Frailty in Older Patients undergoing Emergency Laparotomy: Results from the U.K. observational Emergency Laparotomy and Frailty (ELF) Study.

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Contributions.

LP and SJM conceived and designed the study in addition to obtaining funding. KLP, JL, JH, JMB, PC, IM, ISF, JH and SJM coordinated the trial. KLP, JL, BC and SJM prepared the first draft of the manuscript and were responsible for the final manuscript. KLP, LP, JL, JMB, PC, IM, ISF, JH and SJM developed the protocol. Local investigators at each site recruited patients. BC authored the statistical analysis plan and carried out the analysis. KLP, JL, BC, JH, LP and SJM interpreted the data. All authors revised manuscript drafts, approved the final manuscript, and contributed intellectually important content. SJM is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to published article.

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Mini-abstract

This multicentre study found frailty in 20% of older adults (≥65 years) undergoing emergency laparotomy. Independent of age, increasing frailty was associated with a significantly greater risk of 30- and 90-day mortality, in addition to a greater risk of complications and longer length of critical care and overall hospital stay.

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Structured Abstract

Objective This study aimed to document the prevalence of frailty in older adults undergoing emergency laparotomy (ELAP) and to explore relationships between frailty and post-operative morbidity and mortality.

Summary Background Data The majority of adults undergoing ELAP are older adults (≥65 years) that carry the highest mortality. Improved understanding is urgently needed to allow development of targeted interventions.

Methods An observational multi-centre (n=49) U.K. study was performed (March to June 2017). All older adults undergoing ELAP were included. Pre-operative frailty score was calculated using the progressive Clinical Frailty Score (CFS): 1 (very fit) to 7 (severely frail). Primary outcome measures were the prevalence of frailty (CFS 5-7) and its association to mortality at 90-days post-operative. Secondary outcomes included 30-day mortality and morbidity, length of critical care and overall hospital stay.

Results 937 older adults underwent ELAP: frailty was present in 20%. 90-day mortality was 19·5%. After age and sex adjustment, the risk of 90-day mortality was directly associated with frailty: CFS 5 aOR 3.18 (95%CI 1·24 to 8·14) and CFS 6/7 aOR 6·10 (95%CI 2·26 to 16·45) compared to CFS 1. Similar associations were found for 30-day mortality. Increasing frailty was also associated with: increased risk of complications, length of ICU and overall hospital stay.

Conclusion A fifth of older adults undergoing ELAP are frail. The presence of frailty is associated with greater risks of post-operative mortality and morbidity and is independent of

age. Frailty scoring should be integrated into acute surgical assessment practice to aid decision-making and development of novel post-operative strategies.

INTRODUCTION

Emergency abdominal surgery is performed in every acute hospital in the United Kingdom (U.K.), with the common aim to prevent death and minimise life-altering complications. The majority of these emergency laparotomies are performed on older adults (65 years and older) that when compared to younger adults, have the highest post-operative mortality and morbidity, the highest utilisation of intensive care resources and subsequently, longer lengths of hospital stay. [1-4] This older adult population has a pre-disposition to more complex clinical needs than younger adults as a consequence of a higher prevalence of multi-morbidity, cognitive impairment, polypharmacy and frailty.[5,6] However, there is a paucity of good quality research to improve understanding of this expanding older adult population undergoing emergency surgery with many widely used prognostic indicators and tools having been developed from younger, healthier and often elective patient cohorts. [7-15]

Frailty is defined as an objective measure of increased vulnerability and decreased physiological reserve, resulting from the age-associated accumulation of physiological deficits in multiple systems.[16] Frailty results in diminished resilience to physiological insult such as surgery, preventing or impairing recovery and return to pre-existing functional level. In the medical setting where much prior work has focused, routine frailty assessment for older adult admissions has been accompanied by interventions to modify frailty such as the Comprehensive Geriatric Assessment (CGA). The application of the CGA, that can include medical management, physiotherapy, nutrition, pharmacy and occupational health, has led to improved patient survival and an ability to return to pre-admission residence. [17,18,19] Similar

improved outcomes have been reported in patients with hip fractures as a result of orthogeriatrics input within the first 72 hours of hospital admission. [20,21] In the emergency general surgery setting, two recent meta-analyses assessing the influence of frailty on older adults documented that the presence of frailty (ranging from 0·5 % to 67·2%) led to significant increases in 30-day mortality, complications and length of hospital stay.[22,23] However, the inclusion of lower risk elective surgical patients and acute surgical patients managed conservatively, means the prevalence of frailty and its influence on post-operative outcomes in the high-risk emergency laparotomy setting remains unclear.

The primary aims of the Emergency Laparotomy and Frailty (ELF) Study were to determine the prevalence and influence of frailty on 90-day mortality in older adults undergoing emergency laparotomy. The influence of frailty on post-operative outcomes including 30-day mortality, morbidity and length of hospital stay were evaluated as secondary aims.

METHODS

From 20th March to 19th June 2017 all older patients (defined as 65 years and older) undergoing emergency laparotomy at forty-nine registered sites across the U.K. were screened for inclusion into the ELF Study.[13] This multi-centered prospective cohort study was conceived, designed and led by two established research collaboratives: The North West Research Collaborative (NWRC – www.nwresearch.org) and The Older Persons Surgical Outcomes Collaboration (OPSOC – www.opsoc.eu).

Ethical approval was obtained from National Health Service Research Ethics Committee (Black Country Research Committee: November 2016; 16/WM/0500). The study was registered centrally with the Health Research Authority (England), the NHS Research Scotland Permissions Co-coordinating Centre (Scotland) and the Health and Care Research Permissions Service (Wales). The ELF study was registered online at www.clinicaltrials.gov (NCT02952430).

Site recruitment

Participation from sites across the U.K. was invited using a presentation at the National Research Collaborative meeting in 2016 (www.nationalresearch.org.uk) and the use of social media (@ELFStudy). Fifty-six surgical centers from England, Scotland and Wales registered with data collection received from 49 of those sites.

Patients

The full protocol was published in October 2017 according to STROBE Guidelines.[24,25] Inclusion criteria were consistent with the established U.K. National Emergency Laparotomy Audit [NELA; www.nela.org.uk/criteria].[1] In general, older patients were included if undergoing an expedited, urgent or emergency surgical abdominal procedure for gastrointestinal pathology (laparoscopic or open procedure) and/ or returning to theatre for any major post-operative complication/dehiscence [Appendix 1]. The classification of Intervention was defined according to the National Confidential Enquire into Patient Outcome and Death (NCEPOD) resulting in elective procedures being excluded.[26]

Data Collection

Pre-operatively, each older adult had the following recorded: age and gender; number of co-morbidities (allowing calculation of Charlson Co-morbidity index, CCI)[8,9]; care level/ independence status (selected from home without carers, home with carers, residential home, nursing home, intermediate care, other) and polypharmacy (5 or more current medications). ASA grade (American Society of Anesthesiologists Grade)[10] and P-POSSUM score were calculated as both are routinely collected as part of the NELA.[11,12] The indication for surgery was documented and in theatre, the procedure performed recorded.

Post-operatively, each patient completed 90-day follow-up. For the first 30 post-operative days, mortality was also recorded in addition to: post-operative complications; length of

critical care stay (level 2 High Dependency Unit, HDU and level 3 Intensive Care Unit, ICU); overall length of hospital stay and readmission to hospital.

Completed anonymous datasets were entered into a specifically designed online secure electronic database (REDCap, www.project-redcap.org) developed and maintained by the North West Surgical Trials Centre (www.nwstc.org.uk).

Frailty Scoring

Each patient's surgical or nursing team assessed frailty pre-operatively as part of standard care. The Clinical Frailty Score (CFS) developed by the Canadian Study of Health and Ageing (CSHA) was used [Appendix 2].[27] This 7-point progressive score was developed within an older adult population and is based on clinical judgment with a score of 1 to 4 being classified as non-frail and 5 to 7 as frail. The CFS has been found to be a valid and reproducible score that is simple to understand and apply. OPSOC has used the CFS previously in the emergency surgical population to assess frailty.[28]

Data Completion and Validation

Regular emails to each registered site and Tweets were used to motivate data collection and update ELF Collaborators. To ensure accurate data collection, data validation was performed on 25% of data fields for 10% of cases at each site after study completion.

Statistical analysis

Sample size justification from previous publication: To detect a 10% difference in 90-day post-operative mortality between frail and non-frail patients (7·5% versus 17·5%), a sample size of 480 was required to maintain 80% power and 5% significance .[28]

The primary analysis was performed using a multi-level logistic regression of 90-day mortality by frailty, adjusted for age (65–74, and >75 years old) and gender. Each recruiting hospital was fitted as random effects to account for site variation. A secondary analysis of the primary outcome was carried out by presenting the crude odds ratio (OR), and adjusted OR (aOR) with associated 95% CIs and p values. Length of stay was analyzed with a zero inflated negative binomial regression, and presented as the mean increased length of stay (in whole day integers) with associated 95% CI. We carried out an exploratory analysis to investigate the distribution of day 90 mortality, within age and frailty to determine if our findings could be explained in part by patient age. Statistical analyses were carried out using Stata 14 (StataCorp; www.stata.com).

Patient and Public Involvement

There was no patient and public involvement in this study as it was an observational study in a novel research area.

RESULTS

Patients and Procedure

A total of 956 older adults undergoing emergency laparotomy were recruited to the study. Nineteen patients were excluded due to incomplete or incorrectly entered data, leaving 937 patients in the final analysis [Figure 1].

Table 1 displays the pre-operative patient characteristics by frailty score. Overall frailty (CFS 5,6 and 7) was present in 20% of older adults undergoing emergency surgery. The mean age of the patients was 76 years (SD 6.82; range 65 – 99) with over a third (38%) aged 80 or older. Eighty-nine percent of older adults had documented co-morbidity; 54% poly-pharmacy and the majority (83%) were admitted from home without carers. Two thirds of patients (66%) were ASA 3 or more.

The most common indication for surgery was intestinal obstruction (54%). The commonest surgical procedure performed was adhesiolysis (25%) with the majority of surgery performed by an open approach (87%) [Table 2]. These findings are in keeping with the NELA 4th report.[1] Fifty percent of patients had a post-operative complication, with the median length of hospital stay being 13 days (IQR 7-24). 13·7% (123/ 899) of patients required readmission to hospital within 30 days of discharge.

Frailty and 90-day Post-operative Mortality

Overall 90-day mortality for all patients was 19·5% (183/930). As the frailty score increased the risk of 90-day mortality increased: patients scoring CFS 6 and 7 had the highest risk of 90-day mortality (OR 5·89, 95% CI 2·19 to 15·86; p=0·001) compared to patients scoring CFS1 [Table 3 and Figure 2]. After accounting for patient age and sex, increasing frailty was still associated with increased risk of 90-day mortality: aOR for patients who were mildly frail (CFS 5) and moderately/ severely frail (CFS 6/7) was 3·18 (95%CI 1·24 to 8·14; p=0·016) and 6·10 (95%CI 2·26 to 16·45; p<0·001) respectively compared to CFS 1 (very fit).

Frailty and Secondary Outcomes

Overall 30-day mortality for all patients was 14·6% (137/ 937) and a similar association with frailty was seen for 30-day mortality as for 90-day mortality: CFS 5 aOR 9·79 (95%CI 2·23 to 42·91; p=0.002) and for CFS 6/7 aOR 10·40 (95%CI 2·24 to 48·18; p=0·003) [Table 3]. Increasing frailty score was associated with increased risk of post-operative complications: aOR for CFS 5 was 4·56 (95% CI 2·17 to 9·60; p=0·001) and 3·92 (95%CI 0·35 to 4·19; p=0·001) for CFS 6/7 compared to those older adults scoring CFS 1.

There was increased length of post-operative hospital stay and stay in ICU in frail patients [Table 3]. For hospital stay: aOR for CFS 5 was 1·44 (95% CI 1·10 to 1·89; p=0·008) and 1·62 (1·19 to 2·20; p=0·002) for CFS 6/7compared to adults scoring CFS 1. For ICU length of stay: CFS 5 aOR of 2·15 95%CI 1·15 to 3·96; p=0·02) and CFS 6/7 aOR 4·18 (95% CI 2·11 to 8·03; p<0·001)

compared to CFS 1. Frail patients stayed in ICU for 2 days (IQR 1-4) versus 1 day (IQR 0-3) for non-frail. There was no association with frailty to the length of time in HDU or to 30-day re-admission.

Frailty, by Age mortality distribution

Tables 4A and 4B show that frailty is distributed throughout the range of ages and not restricted to the very old age patient groups (85+). Observation of this distribution shows that patients with a higher frailty score had a higher mortality rate. The marginal 90-day mortality rates were increased from 11.1% to 50% for CFS of 1 to 7 and the marginal mortality rate for increased patient age was 15.9% to 25.3% for patients aged 65-70, compared to those aged 85-90 [Table 4A]. Similar results were found for the 30-day mortality showing that frailty results in a wider distribution of predicted mortality than age [Table 4B]. In addition when compared to P-POSSUM, it can be seen that frailty stratifies the older adult into a greater number of prognostic groups and also allows risk-prediction of 30-day morbidity through the range of scoring, whilst P-POSSUM does not [Table 5].

DISCUSSION

This study is the first to prospectively document the prevalence of frailty in older adults undergoing emergency laparotomy. Frailty was present in a fifth of patients pre-operatively placing them at significantly greater risk of 30- and 90-day mortality. In addition, as the frailty score increased, so did the risk of post-operative complications, and the length of stay in intensive care and in hospital overall. With frailty found to be independent of age, this work supports integration of frailty scoring to all older adults admitted as a surgical emergency to guide peri-operative strategies for this high-risk complex population.

There are several strengths to this work. First, it focused solely on a large population of older patients undergoing emergency laparotomy improving understanding of this overlooked group that carry the highest risk for post-operative death. Second, the data was collected prospectively and was multi-centred minimising geographical bias that could occur with local or regional studies. Third, validation of a proportion of each site's data optimised data completion. Finally, the Clinical Frailty Score (CFS) appears to be a simple tool to use with only a small percentage of frailty scores not entered despite the substantial over-recruitment.

The authors cannot exclude selection bias where a local recruiter may have not contributed a consecutive series of older patients undergoing emergency laparotomy. This is likely to reflect the pragmatic nature of this work. In addition, only a small proportion of patients undergoing

surgery had the highest frailty score (CFS 7), perhaps as a consequence of being unfit for surgery. To overcome this, CFS 6 was combined with CFS 7 for statistical analysis where appropriate.

Previous work in the emergency surgical setting has found frailty to be associated with a greater risk of mortality and longer hospital stays. [28,29,30,31] However, direct comparisons to this current work are difficult due to their limitations of: retrospective analysis; single center only; inclusion of non-operatively managed older adult patients and/ or small patient numbers. In a recently published prospective multi-centered U.K. study (n=2,279) assessing all patients admitted to an acute surgical unit, frailty was found to exist in all age groups and was not exclusive to the older adult population.[32] This study included patients regardless of whether an operation was performed (62% had non-operative management), however the finding of frailty to be independent of age with an almost linear relationship to 90-day mortality is consistent with our study. Furthermore, with our results also showing incremental increases in frailty scores predict greater risks of post-operative complications and longer hospital stays, we believe that the CFS should be interpreted as an individual score rather than the traditional binary classification of frail or not frail.

Clinicians have long been interested in prognostic scores resulting in many being available. All have their limitations in the older adult emergency laparotomy setting including: predicting mortality only (APACHE II, ASA); multiple variables making calculation labor intensive (APACHE

II); not validated in older adult populations (Charlson, ASA); being based on diagnosed co-morbidity with no attempt to differentiate well-controlled morbidity from severe functionally limiting morbidity (Charlson) or requiring intra-operative details to complete score (P-POSSUM).[7-12] Indeed, NELA and The Royal College of Surgeons of England have acknowledged and circumvented such limitations by using P-POSSUM or an equivalent to define a high-risk patient to trigger specific process pathways rather than to determine prognosis.[1,15] The Clinical Frailty Score in comparison predicts both morbidity and mortality, is straightforward to calculate, is validated in older adult surgical populations and can be determined pre-operatively.

Implications for clinicians and policymakers

Frailty scoring should be performed pre-operatively on all older adults undergoing an emergency laparotomy to aid with the complex decision-making and peri-operative care. Few of the already established prognostic scores are easy for the patient and their family to understand, which is potentially detrimental to shared decision-making.[33,34] In contrast, frailty is a concept of which many members of the public may be aware. This underlying knowledge may provide a platform for improved understanding with patients and their family members when discussing not only their operative risks of dying, but of having significant life-altering complications and a prolonged and difficult recovery.

Once the decision for surgery is made, the frailty score could lead targeted peri-operative pathways. For example, patients with CFS 4 to 7 have the highest risk of mortality where early

involvement and assessment by critical care would optimise post-operative planning. Treatment over the first few days post-operatively is focused on continuing treatment for the initial pathology (e.g. sepsis, renal support, ventilator support, wound management) led by critical care and surgeons. This could be improved by working alongside geriatricians and the CGA with the key aim of minimising any complications from frailty.[1,6,15,35] For example: protecting muscle mass (early mobility or movement whether on or off a ventilator); maintaining respiratory capacity (timed regular physiotherapy); nutrition and energy balance (parental or enteral). In contrast, a patient CFS 3 might only spend a short time in critical care before continuing their targeted rehabilitation prescribed by a hospitalist or geriatrician, but led by the surgical ward nurses. This modified emergency laparotomy CGA creates an opportunity for targeted training within both surgical and geriatric curriculums to allow multidisciplinary peri-operative care.[6,36]

CONCLUSION

Frailty is present in 20% of older adults undergoing emergency laparotomy and is independent of age. As frailty increases, the older adult is at greater risk of post-operative mortality and morbidity. These findings support the integration of pre-operative frailty assessment and identify the urgent need to develop novel post-operative strategies to improve outcomes for this complex high-risk group of health service users.

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Figure 1: ELF Study flow diagram.

Table 1: Characteristics of Older Adults undergoing Emergency Laparotomy, by Frailty score.

Table 2: Indication and type of surgical procedure performed on Older Adults undergoing emergency laparotomy.

Table 3: Frailty and Primary and Secondary outcomes in Older Adults undergoing Emergency Laparotomy.

Figure 2: Scatterplot displaying the relationship between Frailty and 90-day mortality in Older Adults undergoing Emergency laparotomy.

Table 4A: The distribution of 90-Day mortality within Frailty by age in Older Adults undergoing Emergency Laparotomy.

Table 4B: The distribution of 30-Day mortality within Frailty by age in Older Adults undergoing Emergency Laparotomy.

Table 5: Comparison of Frailty status to P-Possum by Actual 30-day Mortality and Morbidity.

Appendix 1: National Emergency Laparotomy Audit (NELA) Inclusion and Exclusion Criteria [1].

Appendix 2: The Clinical Frailty Score (CFS) developed by the Canadian Study of Health and Ageing (CSHA).